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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,567	04/07/2005	Alan Barge	056291-5203	8992

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EXAMINER	
FINN, MEGHAN R	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,567	BARGE, ALAN	
	Examiner	Art Unit	
	MEGHAN FINN	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4,5 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 4-5, 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's Amendment filed June 04, 2008 has been received and entered into present application. Claims 1, 3, 6-9, and 11-14 were canceled and no claims were added by applicant. Thus claims 2, 4-5, and 10 are pending.

Applicants' arguments, filed June 04, 2008, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 4, and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bruns et al (Effect of the Vascular Endothelial Growth Factor Receptor-2 Antibody DC101 Plus Gemcitabine on Growth Metastasis and Angiogenesis of Human Pancreatic Cancer Growing Orthotopically in Nude Mice), in view of Sepp-Lorenzino et al. (Antiangiogenic agents targeting vascular endothelial growth factor and its receptors in clinical development), each already of record, for the reasons set forth at pages 9-11 of previous office action dated December 04, 2007, of which reasons are herein incorporated by reference.

In claim 2, applicant claims a method for treatment of pancreatic cancer, comprising administering ZD6474 and gemcitabine. As discussed in the office action dated December 04, 2007, Bruns et al. teaches using gemcitabine with a VEGF-R2 antibody agent DC101 to treat pancreatic cancer (page 101, column 2, paragraph 2). Bruns et al. also teach that inhibition of VEGF R-2 is an effective way to inhibit angiogensis (page 101, column 2, paragraph 1) and that both KDR and VEGF-R2 receptors are involved in vessel growth and pancreatic cancer (page 101, column 1, paragraph 1), however, they do not teach the combination of ZD6474 with gemcitabine. Sepp-Lorenzino et al. teach many different VEGF inhibitors and their use in inhibiting angiogensis (abstract). Specifically they teach that ZD6474 is a Potent KDR receptor

inhibitor (page 1453, section 2.3, line 1) and that ZD6474 inhibits vascular permeability (page 1454, column 1, paragraph 2). Sepp-Lorenzino et al. also teach several VEGF inhibitors are used in combination with gemcitabine, SU5416 (page 1450, column 2, paragraph 4) and CEP-7055 (page 1455, column 2, paragraph 1). They further teach that the same antiangiogenic agents which act on KDR receptors also act on VEGF R-2 receptors (page 1448, figure 1). Thus, it would have been obvious to one or ordinary skill in the art at the time of the invention to substitute ZD6474 (a VEGF inhibitor which acts at KDR) for DC101 (a VEGF-R2 inhibitor) in the method of Bruns et al. since ZD6474 is known to treat vascular permeability and both compounds Inhibit the same VEGF receptor. It is common practice in optimization of cancer therapies to substitute a drug that has good efficacy for the same receptor if it would also have other benefits (known ability to reduce vascular permeability). Thus claim 2 is unpatentable over Bruns et al. in view of Sepp-Lorenzino et al.

In claims 4 and 5, applicant claims a composition and a kit, comprising ZD6474 and gemcitabine. As discussed previously, since the method of using such a composition or kit is unpatentable as discussed above, the composition or kit itself would also be unpatentable over Bruns et al. in view of Sepp-Lorenzino et al.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bruns et al (Effect of the Vascular Endothelial Growth Factor Receptor-2 Antibody DC101 Plus Gemcitabine on Growth Metastasis and Angiogenesis of Human Pancreatic Cancer Growing Orthotopically in Nude Mice), in view of Sepp-Lorenzino et al. (Antiangiogenic

agents targeting vascular endothelial growth factor and its receptors in clinical development), in further view of Ostruszka et al. (The Role of Cell Cycle Progression in Radiosensitization by 2',2'-difluoro-2'-deoxycytidine), each already of record, for the reasons set forth at pages 11-13 of previous office action dated December 04, 2007, of which reasons are herein incorporated by reference.

In claim 10, applicant claims a method of treating pancreatic cancer with ZD6474, gemcitabine, and ionising radiation. As discussed previously, neither Bruns et al. nor Sepp-Lorenzino et al. teach using their combinations with ionizing radiation, however it is a common practice in the art to combine anti-cancer drugs with ionising radiation, such as the example taught by Ostruszka et al., which teaches a combination of ionizing radiation and gemcitabine, as well as the fact that gemcitabine is a radiosensitizer (abstract). Thus one of ordinary skill in the art at the time of the invention would be aware of ionising radiation and the fact that it works in combination with anti-cancer drugs such as gemcitabine, and thus it would have been obvious to one of ordinary skill at the time of the invention two also add ionizing radiation to the combination therapy in claim 10 which is unpatentable over Bruns et al. in view of Sepp-Lorenzino et al., in further view of Ostruszka et al.

Response to Arguments

For both 35 USC 103(a) rejections, applicant has argued that unexpected results as a way to overcome the rejections. In the case of claims 2, 4, and 5, applicant has

argued that the results shown in Table 1 of the specification (page 14), along with a paper by Conrad et al., which reports the same table, indicates that the combination of ZD6474 and Gemcitabine is unexpectedly better than the agents by themselves. This is not found to be persuasive. In table 1, applicant shows a tumour weight average for the control which is 1231mg, the average tumour weight with ZD6474 is 541 ±201mg which ranges from 340mg to 742mg. The average tumour weight for the combination of ZD6474 and gemcitabine is 308 ±129mg, which is a range of 179-437mg. Thus average tumour weight is not statistically different between ZD6474 and the combination.

Additionally, applicant has compared their combination to the two drugs by themselves, but since they are administered in the same concentrations together there is actually 2 times the amount of anti-cancer medication being administered, so one would expect an additive effect. Thus one would expect the combination to be better than the two separately, in order to show unexpected results the increased result should be more than the two together would be expected, such as more than an additive effect. This is clearly not demonstrated in table 1 or any of applicant's disclosure. Furthermore, in order to make an argument for unexpected results, applicant needs to compare their results with the closest applicable prior art, which would be Burns et al. because they teach a combination of a VEGF R-2 inhibitor and gemcitabine. Applicant has not compared their results to any combination therapy involving either of the two drugs in question, and clearly is not comparing their results to the closest prior art.

For the rejection of claim 10 over Burns et al. in view of Sepp-Lorenzino et al. in further view of Ostruszka et al., applicant has again argued unexpected results. Applicant submits Bianco et al. and table 2 (page 7105 of Bianco et al.) as evidence that the combination of gemcitabine and ZD6474 with ionizing radiation is more effective than either drug alone with ionising radiation. As discussed above, applicant has not compared their results to the closest prior art of Burns et al., or any other combination therapy involving the claimed drugs. One of ordinary skill in the art would expected a certain additive effect from the two drugs being combined together, as the same dosages they were used separately, because more anticancer drug is being administered. Gemcitabine and ionizing radiation (RT) reduced the proliferative activity by 42% (from 72% to 30%) and ZD6474 with RT reduced the proliferative activity by 40%. Thus if there was an additive effect, one would have expected the combination therapy to reduce the activity by 82%, which would be a net -10% proliferative activity. Obviously, not all drug combinations will have such a good effect, there is a limit to which more drug will have any effect, but an activity level of 7% (which is what is reported for gemcitabine + ZD6474 + RT) would not be unexpected given the amount of reduction each drug is able to achieve. In light of the fact that the data presented in Bianco et al. is not unexpected, and the applicant fails to compare their invention to the closest prior art (Burns et al.), this argument does not demonstrate unexpected results.

This argument is not deemed persuasive and thus the rejection of claims 2, 4, 5, and 10 is **maintained.**

Conclusion

Rejection of claims 2, 4, 5, and 10 is deemed proper and is **maintained.**

No Claims of the present application are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Meghan Finn whose telephone number is (571) 270-3281. The examiner can normally be reached on 8:30am-6pm Mon-Thu, 8:30am-5pm Friday (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Meghan Finn

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614